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Palladium-Catalyzed Asymmetric Allylic α-Alkylation of Acyclic Ketones

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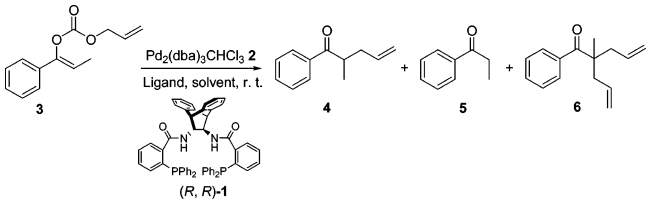
Regio- and stereoselective formation of new carbon−carbon bonds is a fundamental problem in synthetic organic chemistry. One of the important C−C bond formation reactions is the α-alkylation of ketone enolates.[1] However, metal-catalyzed asymmetric alkylation of unstabilized ketone enolates remains one of the most challenging reactions because the enolate equilibration during the reaction can lead to loss of regioselectivity, polyalkylation, and, in the case of creating tertiary centers, racemization of product.[2] While there has been some recent progress in the case of cyclic ketones,[3] to our knowledge, there are no examples of asymmetric alkylation of the conformationally nonrigid acyclic ketones, in which the specific issue of the relationship of enolate geometry to asymmetric induction must be addressed. Herein, we report the first such examples and some mechanistic insights.

We initially selected ligand **1** and $Pd_2(dba)_3CHCl_3$ **2** to catalyze the reaction of (*Z*)-allyl-1-phenylprop-1-enyl carbonate **3** in toluene at ambient temperature (Table 1). The reaction went to completion in 3 h and led to alkylated product **4** in 68% yield and 75% ee. The byproducts detected by GC were ketone **5** and dialkylated product **6** in 24% and 4% yield, respectively. Changing the solvent to THF increased the enantiomeric excess value of the product to 88% but did not improve the yield. One the other hand, improvement occurred by switching to 1,4-dioxane; only 6% of **5** and no dialkylated product were detected by GC. The enantiomeric excess of **4** also increased to 94%. These results are significantly superior to those using dppe or dppb as ligand[4] (Table 1 entries 4−6). Thus, proton transfer is significantly eliminated by using our chiral ligand in 1,4-dioxane.

The reaction scope is summarized in Table 2. In general, excellent yields and enantiomeric excesses were obtained for various aromatic ketones. While the reaction can tolerate a broad range of substitution groups on the aromatic ring, some electronic effect was observed. Substrates bearing a more electron-rich aromatic ring (entries 10 and 13) had better enantiomeric excess (98%) than those possessing more electron-deficient aryl rings (entries 11 and 12, 73 and 82%, respectively). The length of the alkyl chain at R_2 does not affect the results of the reaction (entries 2 and 3). However, an α-branched group significantly slows the reaction and decreases the enantiomeric excess (entry 4). The yield and enantiomeric excess were restored in the case of a *β*-branched R_2 (entry 5). Replacing the aryl ring by a vinyl group retained an excellent yield and high enantiomeric excess (entries 17 and 18). In the challenging case of the unsymmetrical aliphatic ketones, such as **7**, where R_1 = cyclohexyl and R_2 = methyl (Scheme 1), no loss of regioselectivity was observed in both the *E*- and *Z*-enol carbonates,[5] although the *Z* isomer reacted more sluggishly and had a lower enantiomeric excess (60%) than the aromatic (entry 1, 94%) or enone (entry 17, 88%) cases, even though the steric size of these three R_1 groups should be close. This may suggest that the enantiorecognition step involves not only steric effects of R_1 and R_2 but also some electronic effects, such as *π*-stacking interactions, between the substrate and the ligand.

By using (*E*)-allyl-1-cyclohexyl-1-propenyl carbonate (Scheme 1) as the substrate, we can generate the corresponding monoallyl alkylated aliphatic ketone in almost quantitative yield exclusively as one regioisomer in 97% ee. The double bond geometry of the enol carbonate **7** controls not only the enantiomeric excess but also the configuration of the resulting ketone (see Scheme 1). The double bond geometry also affects the reaction rate. Thus, (*E*)-**7** was more reactive than its *Z* isomer. The same effect was also observed in

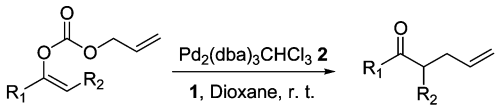
Table 1. Selected Optimization Studies[a]

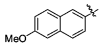


entry	ligand	solvent	time	yield% (ee) of **4**	yield% of **5**	yield% of **6**
1	**1**	toluene	3 h	68 (75%)	24	4
2	**1**	THF	1 h	61 (88%)	25	14
3	**1**	dioxane	30 min	94 (94%)	6	0
4	dppe	dioxane	10 min	61	24	14
5	dppb	dioxane	10 min	67	20	13
6	dppb	toluene	3 h	53	38	9

[a] Unless otherwise indicated, all reactions were performed at 23 °C on a 0.3 mmol scale at 0.1 M using 2.5 mol % of **2** and 5.5 mol % of ligand; yields are determined by quantitative GC analysis using decane as internal reference; enantiomeric excess of **4** was determined by chiral HPLC on a ChiralcelOD-H column eluted with 2000:1 heptane:2-propanol.

Table 2. Reaction of Various Allyl Enol Carbonates of Acyclic Ketones[a]

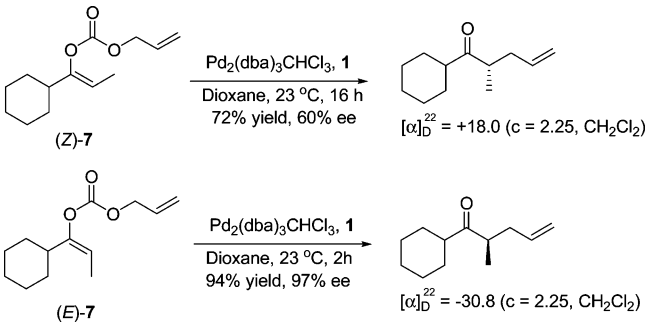


	R_1	R_2	*Z*/*E*[b]	time	yield	ee
1	Ph	Me	>98/2	2 h	94%	94%
2	Ph	Et	>98/2	2 h	94%	94%
3	Ph	C_5H_{11}	>98/2	16 h	93%	92%[c]
4	Ph	*i*-Pr	>98/2	24 h	30%	32%[c]
5	Ph	CH_2Ph	>98/2	1 h	75%	88%
6		Me	>98/2	1 h	90%	95%
7	2'-F-Ph	Me	>98/2	1 h	80%	94%
8	3'-Cl-Ph	Me	>98/2	1 h	97%	93%
9	4'-Br-Ph	Me	>98/2	1 h	94%	93%
10	2'-OMe-Ph	Me	>98/2	16 h	99%	98%[c]
11	Pyridyl	Me	>98/2	1 h	95%	73%[c]
12	3'-NO_2-Ph	Me	>98/2	1 h	83%	82%
13	Furyl	Me	>98/2	4 h	89%	88%
14	2'-CF_3-Ph	Me	>98/2	2 h	94%	92%
15	Mesityl	Me	5/95	6 h	99%	96%[c]
16	Mesityl	Me	96/4	16 h	trace	NA
17		Me	>98/2	5 h	94%	88%
18		Me	25/1	0.3h	93%	91%

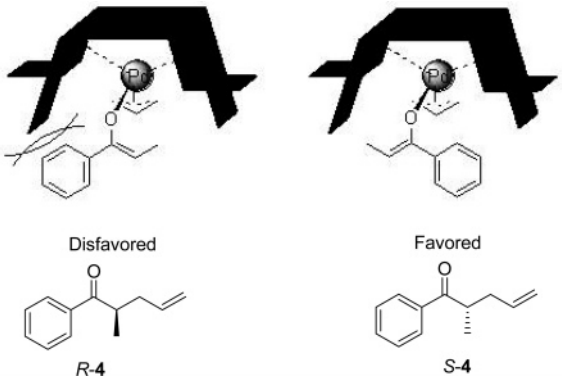
[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M in 1,4-dioxane at 23 °C using 2.5% **2** and 5.5% ligand **1**; the yields were isolated yields, and enantiomeric excess values were determined by chiral HPLC. [b] *Z*/*E* ratio was determined by ^1H NMR. [c] The enantiomeric excess values were determined by analysis of the derivative described in Supporting Information.

10.1021/ja055968f CCC: $30.25

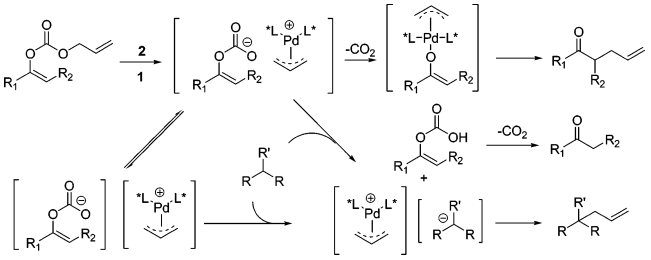
Scheme 1. Double Bond Geometry Controls the Configuration and Enantiomeric Excess of Product



Scheme 2. Model for the Enantioselectivity of **4**



Scheme 3. Proposed Mechanism for the Reaction

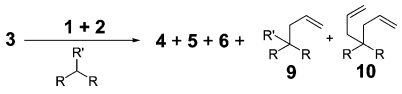


the case of 1-mesityl-1-propenyl carbonate (entries 15 and 16); the reaction of the *E*-isomer went to completion in 6 h with a quantitative yield and 96% ee, but only trace amount of product was detected in 16 h for the *Z* isomer.

The absolute configuration of **4** was determined to be *S* by Pd−$CaCO_3$-catalyzed hydrogenation of the C=C double bond and comparison of the optical rotation of the product with the known enantiomer.[6] This result conflicts with the model of intermolecular nucleophilic attack of the enolate on the π-allyl−Pd complex possessing ligand **1**, by which the *R* enantiomer is preferred.[7] The same conflict was found in our previous studies.[3a] In the case of allyl enol carbonate, since the π-allyl−Pd cation is the only counterion of the in situ generated enolate, it is likely that there is coordination between the enolate and palladium. According to the work of Hartwig et al., either C- or O-bound arylpalladium enolates can undergo reductive elimination to generate the corresponding α-aryl ketones.[8] Therefore, under our reaction conditions, a reasonable explanation invokes a shift of mechanism from a direct attack of the enolate on the allyl moiety to an inner sphere process of coordination and reductive elimination (Scheme 2).

The distinctive solvent effect in favor of 1,4-dioxane may be explained by the fact that it is much better in forming solvent caged contact ion pairs than THF.[9] The proton sources in the bulk solution, mainly the monoalkylated product itself or trace amounts of water,

Table 3. Reactions with Proton Sources



entry	R	R′	solvent	time (min)	**4** (% ee)	**5** (%)	**6**(%)	**9** (%)	**10** (%)
1	CO_2Me	Me	dioxane	30	94 (94)	6	0	0	0
2	CO_2Me	H	dioxane	15	90 (93)	10	0	9	0
3	$COCH_3$	H	dioxane	15	17 (81)	83	0	91	0
4	CO_2Me	H	THF	10	71 (87)	27	2	22	0
5	$COCH_3$	H	THF	<5	8 (63)	92	0	76	14

may react more slowly in 1,4-dioxane relative to collapse to product, so that very little proton transfer occurs between the enolate and these proton sources. The conjecture is supported by the reaction of **3** in 1,4-dioxane in the presence of 1 equiv of dimethyl methylmalonate, dimethyl malonate, or acetylacetone. The reaction with dimethyl methylmalonate was identical to that of the control. A small amount (9%) of dimethyl allylmalonate was detected in the run with dimethyl malonate, and the yield of byproduct **5** slightly increased to 10%, but the enantiomeric excess of the reaction remained high (93%) (entry 2). In entry 3, high yields of **5** (83%) and allyl acac (91%) were detected with the loss of yield (17%) and enantiomeric excess (81%) of the product **4**. A similar trend was observed in THF, with the addition of a significant amount of diallyl acac also being observed. With the increase of the acidity of the additive, the ability to intercept the solvent caged contact ion pair relative to collapse to **4** increases. Thus the amount of byproducts increases.

In summary, we report the first palladium-catalyzed asymmetric α-allyl alkylation of acyclic ketones. The reaction proceeds under very mild conditions and generates an α-tertiary stereogenic center with excellent yield, regioselectivity, and enantiomeric excess. On the basis of our experimental results, we propose an intramolecular mechanism involving an inner sphere reductive elimination, quite distinct from the usual behavior of π-allyl−Pd complexes. Further investigation of the mechanism and the application of the reaction in organic synthesis are underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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